Remarks

The Office Action mailed May 20, 2003 has been received and reviewed. Claim 25 having been amended, the pending claims are claims 1-34. Claims 1-24 and 30-34 have been withdrawn from examination by the Examiner, such that claims 25-29 are presently under examination. Reconsideration and withdrawal of the rejections are respectfully requested

The amendment to the specification at page 7, line 28, is supported by the specification at, for instance, page 6, lines 6-8. The amendments to the specification at the paragraphs beginning at page 2, line 24; page 3, line 11; page 3, line 22; page 4, line 28; page 5, line 16; page 8, line 3; and page 8, line 26 are supported by the specification at, for instance, page 6, lines 6-8. The paragraph beginning at page 16, line 4, is amended to correct a clerical error. The paragraph beginning at page 19, line 14, is amended to correct an obvious error.

Claim 25 is amended to delete to first recitation of the word "virus."

Applicants agree with the statement at page 7 of the Action that the prior art does not teach or suggest the claimed invention.

Objections to the Disclosure

Applicants respectfully disagree with the assertion that the title of the invention is not descriptive. However, in the interests of furthering prosecution, the title has been amended to recite "METHODS FOR IDENTIFYING POLYPEPTIDES THAT PREVENT CELL DEATH."

The Action notes that Figure 2 is referred to in the Brief Description of the Drawings section of the specification, but the drawings filed have Figure 2A, Figure 2B, and Figure 2C. Applicants respectfully disagree. The paragraph in the Brief Description of the Drawings section of the specification beginning at page 6, line 10, discloses "2A" at line 10, "2B" at line 11, and "Figure 2C" at line 15. Thus, the description of Figure 2 at page 6 correlates to Figure 2 as filed. To further prosecution, the paragraph beginning at page 6, line 10, has been amended to disclose "Figure 2A" and "Figure 2B."

The paragraph beginning at page 6, line 10 of the specification has been amended to include a period at the end of the last sentence.

The Action notes that the statement at page 2 is confusing. Applicants respectfully disagree. However, in the interests of furthering prosecution, the specification has been amended at the paragraph beginning at page 7, line 17, to disclose the relationship between the amino acids of SEQ ID NO:1 are the amino acid 119-275 of the carboxy terminal portion of the VEE capsid polypepitde available at GenBank Accession Number L01443. The remainder of the specification has also been amended to reflect the change at the paragraph beginning at page 7, line 17. Specifically, the paragraphs beginning at page 2, line 24; page 3, line 11; page 3, line 22; page 4, line 28; page 5, line 16; page 8, line 3; and page 8, line 26 have been amended to delete "SEQ ID NO:1" and insert therefor the phrase "the carboxy terminal portion of the VEE capsid polypeptide available at GenBank Accession Number L01443."

The Examiner is respectfully requested to reconsider and withdraw the objections to the specification.

Drawings

The drawings included with the present application at the time of filing are objected to by the Draftsperson. Further, the proposed drawings mailed January 28, 2002, have been disapproved as not complying with the provisions of MPEP §608.02(v). Applicants respectfully submit herewith the same Drawings that were originally mailed January 28, 2002. Under the recent revisions to 37 C.F.R. §1.121(d), it is Applicants' understanding that a marked-up copy of any amended drawing is no longer required. Figures 1, 2A, and 3 have not been amended. Figures 2B and 2C have been amended to include the appropriate sequence identifiers.

As noted in the Preliminary Amendment mailed January 28, 2002, Figure 2B has also been amended to include two bases. Specifically, the following text, which is located in the lower right hand side of the figure,

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(XhoI)
CTCGA
CTCGA
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has been amended to add a "G" at the end of each of the line,

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(XhoI)
CTCGAG
CTCGAG
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Support for these corrections is found in SEQ ID NOS: 31, 32 and 12 of Figures 1 and 2A as originally filed.

Applicants respectfully submit that the Replacement Sheets of the Drawings included herewith comply with 37 C.F.R. §1.84 and §1.152. Further, in view of the addition of the sequence identifiers to Figures 2B and 2C, Applicants respectfully submit that the present patent application now complies with the requirements of 37 C.F.R. §§1.821-1.825.

Acceptance of the newly submitted Drawings and reconsideration and withdrawal of the objections to the Drawings is respectfully requested.

The 35 U.S.C. §112, First Paragraph, Rejection

The Examiner rejected claims 25-29 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is respectfully traversed.

Applicants agree with that statement at page 6 of Office Action that "the specification indeed provides guidance to making [] collections of polypeptides comprising a fragment of the VEE capsid protein and introduce them into cells . . . ." The specification also teaches that a polypeptide of the present invention can be expressed in cells. Such polypeptides are typically

encoded by a polynucleotide that can be present in a cell in a vector (specification, page 19, lines 14-21). Vectors useful for this purpose are disclosed in the specification at, for instance, page 12, line 18 through page 15, line 1, and a prophetic example describes the use of a retroviral vector to introduce and express in cells polynucleotides encoding the polypeptide collections (Example 2).

The Action asserts that the specification "fails to provide sufficient guidance with respect to the structures, especially conformations, and properties of the polypeptides . . . ." Regarding the assertion that the specification fails to provide sufficient guidance with respect to conformations of the polypeptide, the Examiner is requested to note that the specification discloses at pages 7 and 8 that the regions of amino acids 129-137, amino acids 182-189, and amino acids 257-264 are present on the surface of the polypeptide. Specifically, each "polypeptide of a collection includes a fragment of an amino acid sequence having a peptide backbone conformation that acts to *display a variable amino acid sequence on the surface of the polypeptide*" (see page 7, lines 17-19). An example of a fragment is the carboxy terminal portion of the VEE capsid polypeptide, which begins at about amino acid 119 and ends at about amino acid 275, and is depicted at SEQ ID NO:1 (see page 7, lines 17-28). The variable amino acid sequence replaces from about 1 to about 4 amino acids within 1 of 3 regions of the fragment. The 3 regions are amino acids 129-137, amino acids 182-189, and amino acids 257-264 of SEQ ID NO:1 (see page 8, lines 3-15). Applicants also disagree with the assertion that the specification fails to provide sufficient guidance with respect to the properties of the polypeptides. The polypeptides encompassed by method claim 25 clearly have the property of preventing cell death (see page 16, lines 4-26).

Regarding the suggestion that the application does not provide guidance as to the structures and components of the pathogens or toxins, it is Applicants' position that such a disclosure is not required to meet the enablement requirement. Further, the Action notes that "the structures, especially conformations, and properties of the polypeptides" and the "structures and components of the pathogens or toxins, as well as their potential interaction with the collection of polypeptides . . . are all critical factors for successfully identifying a polypeptide . .

. ." Applicants respectfully disagree with the assertion that these are "critical factors." An advantage of this method is the ability to obtain polypeptides that prevent cell death without the need for knowledge of the conformations of the polypeptides, or the structures and components of the pathogens or toxins. The notion that these are not "critical factors" is supported by the documents cited in the Action. The two documents cited by the Examiner are considered in the following two paragraphs.

Caponigro et al. (Proc. Natl. Acad. Sci. USA, 95, 7508-7513 (1998)) conducted a large-scale selection for random peptide and protein fragments that cause a specific phenotype, i.e., permitting yeast to escape from α factor-induced cell cycle arrest (Caponigro et al., last paragraph of Introduction section). One of the two libraries produced was a peptide display library composed of 15 amino acid peptides inserted into the green fluorescent protein. These 15 amino acid peptides were random (see last paragraph of Introduction section), and this library was intended to serve as a source of nonnative peptides that could be used subsequently to identify relevant *in vivo* targets (Caponigro et al., first paragraph of Results section). Caponigro et al. did not appear to have a have a specific target for the peptide libraries to interact with, and even if they did, it had no effect on the production of the library: the libraries were random. Thus, Caponigro et al. did not require knowledge of the structures, conformations, or properties of the polypeptides in the libraries, and the structures and components of the targets in the yeast were not required.

Norman et al. (Science, 285, 591-595 (1999)) screened peptamer libraries containing 16 random amino acids inserted into the open reading frame of the staphylococcal nuclease (Norman et al., page 591, col. 2). The ability of members of these libraries to cause a specific phenotype, i.e., inhibition of the pheromone signaling pathway, transcriptional silencing, or the spindle checkpoint, was determined. Like Caponigro et al., the method of Norman et al. did not appear to have a have a specific target for the peptide libraries to interact with, and even if they did, it had no effect on the production of the random libraries. Thus, Norman et al. did not require knowledge of the structures, conformations, or properties of the polypeptides in the

libraries, and the structures and components of the targets in the yeast were likewise not required.

Thus, in order to practice the method of claim 25 as broadly claimed, the skilled person would not require any knowledge of the structures, especially conformations, and properties of the polypeptides of claim 25, and would not require any knowledge of the structures and components of the pathogens or toxins of claim 25, as well as their potential interaction with the collection of polypeptides.

It is respectfully submitted that Norman et al. was partially misinterpreted in the Action. The Action states that "Norman et al. stress . . . the requirement of a reliable test for verifying the potential candidates because of the very high rate of false positives and false negatives" (Action at page 7). This statement incorrectly implies that the method of Norman et al. to identify active members of the libraries had many false positives and false negatives. The statement in Norman et al. at page 594 about false positives and false negatives refers to the two-hybrid analysis system, which was used by those authors *after* identification of a member of a library that caused one of the three specific phenotypes. Specifically, the two-hybrid analysis system was used to determine the target of the identified library member. Thus, the method of Norman et al. to identify active members of the library did not have a very high rate of false positives and false negatives.

The Action notes that the nature of the invention "is complex, especially given the extreme diversity of pathogens and toxins and the high complexity of the structures and properties thereof" (Action, page 6). The Examiner is requested to note that to practice the claimed method, the skilled person must provide a cell containing a polypeptide having the characteristics as recited in claim 25, expose the cell to a pathogen or toxin, and determine whether the polypeptide prevents cell death. The step of determining whether the polypeptide prevents cell death includes incubating the cell and observing if the cell proliferates or not. Each of these steps can be easily practiced by the skilled person using the present specification and the knowledge generally available.

The Action notes at page 8 that "the prior art does not address the predictability of identifying a polypeptide that inhibits a particular biological or cellular pathway." This assertion is plainly wrong in view of the art cited by in the Action. Caponigro et al. disclose that a yeast strain was transformed with the peptide display library composed of 15 amino acid peptides inserted into the green fluorescent protein, and selections for resistance to α factor were carried out. Two different sequences were identified from this library, and 14 different sequences were identified from a second library (see Caponigro et al. at pgae 7510, col. 1, first full paragraph). Norman et al. disclose that transformation of the library into a yeast strain resulted in identification of 3 peptides that inhibited the spindle checkpoint (paragraph spanning pages 591 and 592). Norman et al. also identified 20 peptides that were silencing inhibitors and 9 that inhibited the pheromone signaling pathway (paragraph spanning pages 592 and 593). Thus, one experiment by Caponigro et al. with the random library resulted in identifying 2 polypeptides, one experiment by Norman et al. resulted in either 3, 20, or 9 polypeptides, depending on the phenotype being assayed. Thus, the prior art suggests that there is some predictability to identifying a polypeptide as recited in claim 25.

The Examiner is requested to consider that enablement is not precluded by the necessity for some experimentation, such as routine screening. The key word is "undue" not "experimentation." *In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). In fact, a considerable amount of experimentation is permissible if it is merely routine, or the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should take. *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Bd. App. 1982). Thus, the fact that cells containing a polypeptide as recited in claim 25 would have to be exposed to a pathogen or a toxin and screened to determine whether the polypeptide prevents cell death does not constitute "undue experimentation," particularly in an art where the level of skill is high. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

The Examiner is requested to consider that "not every last detail of an invention need be described in a patent specification, else patent specifications would turn into production specifications, which they were never intended to be." *In re Gay*, 309 F.2d 769, 774, 135 USPQ

311, 316 (CCPA 1962). There is ample guidance in the art and the present specification regarding what a person of ordinary skill must do to practice the invention, e.g., providing a cell containing a polypeptide as recited in claim 25, exposing the cell to a pathogen or toxin, and determining whether the polypeptide prevents cell death.

The first paragraph of §112 requires no more than a disclosure sufficient to enable the skilled worker to carry out the invention commensurate with the scope of the claims. It is respectfully submitted that upon reading Applicants' specification the skilled worker would be able to carry out the invention commensurate with the scope of the claims. The Examiner is respectfully requested to reconsider and withdraw the rejection of claims 25-29 under 37 C.F.R. §112, first paragraph.

The 35 U.S.C. §112, Second Paragraph, Rejection

The Examiner rejected claims 25-29 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. This rejection is respectfully traversed.

The Action asserts the phrase "beginning at any amino acid from about 119 to about 124 and ending at any amino acid from about 258 to about 275" in claim 25 is vague and confusing because it is unclear what the phrase modifies." It is Applicants' position that a person of ordinary skill would recognize that this phrase clearly defines the metes and bounds of the claims. Even if these terms caused the metes and bounds of the claims to not be readily recognizable to one of skill in the art, the meaning of the term is clear in view of the disclosure. The specification discloses that amino acids 119-275 of the VEE virus capsid polypeptide is a carboxy terminal portion of that capsid polypeptide (see, for instance, page 6, legend to Figure 2, and paragraph spanning pages 7 and 8). Thus, a person of skill in the art would readily recognize that the phrase"beginning at . . . and ending at . . . " does not refer to the term "each polypeptide."

Claim objections

Claim 25 has been amended to delete the first occurrence of the term "virus." The Examiner is requested to reconsider and withdraw the objection to claims 25-29.

Summary

It is respectfully submitted that the pending claims 25-29 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

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"Express Mail" mailing label number: EV 073735144 US Date of Deposit: September 22, 2003
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